Cancelled

24. The method of claim 16 wherein the virus is resistant to anti-viral agents that inhibit viral DNA replication.

25. The method of claim 16 wherein cells are virally infected.--

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REMARKS

I. The Claimed Subject Matter

Upon entry of the above-requested amendment, new claims 16 through 25 will be pending in the application. The sole independent claim, 16, corresponds to prior claim 13 and addresses the Applicants' discovery that viral replication in cells is inhibited by contacting cells with a leflunomide product in amounts effective to inhibit the assembly, in cell cytoplasm, of viral virion components such as viral DNA-containing nucleocapsids, tegument, and external proteins. (See particularly Example 5 and Example 8C.) This mechanism of anti-viral action is quite distinct from that prompted by known anti-viral agents which generally interfere with replication of viral DNA or DNA packaging within infected cells, and provides a new tool for treatment of, *e.g.* infections with drug resistant viruses.

Anti-viral activity, including activity against a drug resistant virus, is demonstrated in the specification in the context of *in vitro* assays (Examples 1-6, 8, 9 and 10). The specification also provides, *in vivo* animal model study results (Example 7) and notes the successful treatment of a human patient (page 46, line 13 through page 47, line 8). In the animal and human study, significant decreases in viral load were effected.

Dependent claims 17-25 address presently preferred embodiments of, and contexts for, performance of the method of claim 16. The texts of claims 17-25 respectively correspond to prior dependent claims 2, 3, 5, 6, 7, 8, 9, 10 and 11.

II. Objections and Rejections of Prior Claims 1-13.

The Office Action of October 17, 2001, lodged a formal objection to prior claim 6 (on grounds of improper dependency) and a Section 112, second paragraph rejection of prior claims 8 and 9 (on grounds of asserted indefiniteness).

Prior claims 1, 2, 4, 6, 7 and 12 were rejected under Section 102(b) as assertedly anticipated by U.S. Patent 5,556,870 to Weithmann *et al.* (hereafter, "Weithmann").

Prior claims 1, 2 and 4-13 were rejected under Section 103(a) as assertedly rendered obvious by the disclosures of Weithmann in combination with the disclosures of Flamand *et al., J. Virol., 65:*5105-5110 (1991) (cited as CAPLUS Abstract, AN 1991:581163, hereafter, "Flamand") and/or Hammer, *AIDS, 10:*suppl. 3, s1-s11 (1996) (hereafter, Hammer).

All prior claims (1-13) were additionally rejected under Section 103 as assertedly rendered obvious by the disclosures of Applicant Williams and his co-workers in McChesney *et al., Transplantation, 57:*1717-1722 (1994) (hereafter, "McChesney") in view of WO 94/24095 by Coghlan *et al.*(hereafter, "Coghlan").

III. Grounds for Reconsideration

A. Regarding the Restriction Requirement

In response to the restriction requirement being made final, Applicants have canceled non-examined claims 14 and 15.

B. Regarding Claim Objections

Cancellation of prior claim 6 moots the outstanding objection thereto. New dependent claim 20, which corresponds to prior claim 6, is believed to be in proper dependent form.

C. Regarding Section 112 Claim Rejections

Cancellation of prior claims 8 and 9 moots the outstanding rejection thereof. New dependent claims 22 and 23, which correspond to prior claims 8 and 9, have been reworded in the manner suggested by the Examiner to eliminate any possibility of indefiniteness.

D. Regarding the Section 102(b) Rejection

Cancellation of prior claims 1, 2, 4, 6, 7 and 12 moots the Section 102(b) rejection thereof based on the Weithmann reference. Prior claim 13, which closely corresponds to independent claim 16, was not rejected under 35 U.S.C. §102(b).

E. Regarding the Section 103(a) Rejection
Based on Weithmann, Flamand and/or Hammer

To the extent that prior claims 1, 2 and 4-13 have been canceled, the Section 103(a) rejection thereof is mooted. Inasmuch as the subject matter of prior claim 13 survives in the form of independent claim 16, Applicants submit that no *prima facie* case of obviousness of that subject matter can properly be made out through application of the primary (Weithmann) or secondary (Flamand and/or Hammer) references.

Weithmann contains no disclosure or suggestion that any leflunomide product possesses anti-viral activity. Weithmann asserts only that un-metabolized leflunomide (HWA 486) appears to have activity in modulating secretion of IL-1β by cells, including cells of patients who have various "disorders" resulting in production and circulation of IL-1β.

Moreover, the experimental results set out in Weithmann do not constitute any credible scientific basis whatever for therapeutic utility in animal, including human, "patients." Note first that Weithmann acknowledges that leflunomide (HWA 486) is rapidly metabolized upon administration to form an active metabolite (A771726). (column 1, lines 9-37) As noted in Exhibit A hereto [Lucien *et al., Therapeutic Drug Monitoring, 17:*454-459 (1995)], leflunomide (as opposed to A771726) has low

solubility so the preferred method of administration to the rabbits studied was oral. (See page 458, right column.) As shown in Figure 3, dotted line, plasma concentration of A771726 began to appear and rise in minutes, with peak levels being obtained at approximately 7 hours. Levels thereafter fell off until 25 hours, meaning that by 7 hours the significant kinetic factor was A771726 degradation as opposed to conversion to that metabolite. Moreover, in the rat study described in Exhibit B hereto [Zhang *et al.*, *In:Proceedings of the 47th Conference on Mass Spectrometry and Allied Topics*, pages 1487-1488 (Elsevier Science, New York, NY 1999)] the half-life of leflunomide (SU101) at discontinuation of six hours of infusion was 1.3.± 0.1 or 2.6 ± 0.2 hours depending on IV dose, while the half-life of metabolite (SU0020) was significantly longer and dose independent.

Next Weithmann provides the observation that leflunomide, but not its metabolite, has activity in inhibiting cytokine "synthesis and liberation."

> Thus, it was found, in accordance with the invention, that leflunomide exerts a strong inhibitory effect on the synthesis and liberation of cytokines from blood cells, whereas the leflunomide metabolite does not exhibit this advantageous effect. (Column 1, lines 45-49; Emphasis supplied.)

Weithmann then "demonstrates" an IL-1β reduction effect in a specially-prepared isolated blood cell fraction which has a reduced capacity to metabolize leflunomide. *See* Example 1 and column 3, lines 23-26.

Finally, Weithmann claims the use of leflunomide to treat a variety of diseases (including viral diseases) in "humans and animals" without ever addressing how to prevent leflunomide from being metabolized promptly upon administration! Thus viewed, Weithmann provides, at best, news of a "test tube curiosity" in terms of inhibiting IL-1β production. It contains no disclosure or suggestion of usefulness leflunomide products as viral replication inhibitors.[1]

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[1] It is worthy of note in this respect that the present specification exemplifies leflunomide product effects, including reduction of viral load in a human, through use of the leflunomide metabolite, A771726.

Because the primary, Weithmann reference, contains no suggestion of the viral replication inhibitory methods of claim 16, no *prima facie* case of obviousness can be made out through combination of Weithmann with the disclosures of the secondary reference to Flamand (addressing IL-1β production by virally-infected cells) or Hammer (addressing pyridinyl compounds as anti-retroviral agents).

F. Regarding the Section 103(a) Rejection Based on McChesney and Coghlan

To the extent that prior claims 1-13 have been canceled, the Section 103(a) rejection thereof is mooted. Inasmuch as the subject matter of prior claim 13 survives in the form of independent claim 16, Applicants submit that no *prima facie* case of obviousness of that subject matter can properly be made out through application of the McChesney and Coghlan references.

Significantly, it is not the case that, in the McChesney reference, Applicant Williams and his co-workers teach "that both leflunomide and A771726 are known to be effective in preventing viral infections" as has been maintained by the Examiner. That reference relates to evaluation of immunosuppressive effects of leflunomide alone and in combination with cyclosporine in dogs undergoing kidney allograft transplantation. The principle finding of the study was that leflunomide alone (like cyclosporine alone) was ineffective at the lowest dosage level administered. While leflunomide was effective at intermediate levels up to the highest level (16 mg/kg/day, providing a blood level readily tolerated by humans) the highest levels were in fact toxic to the dogs. When the lowest (independently ineffective) doses of leflunomide and cyclosporine were combined, the longest mean survival time of all (68 days) was achieved. While in the Abstract of the report notes anecdotally that, in dogs treated with a toxic (16 mg/kg/day) dose, "no viral or bacterial infections were noted," this is by no means a statement that leflunomide and A771726 "are known to be effective in preventing viral infection." The experiments reported were not designed to determine anti-viral or anti-bacterial effects of leflunomide. Indeed, the "Materials and Methods" section does not even allude to procedures for

determining the presence or absence of bacterial or viral disease and reference to such disease states is provided only in the Abstract and only with the highest-dosed animals. There was no challenge of the dogs with virus and no reference to the infected/non-infected status of any other experimental or control group. Finally, in accordance with NIH animal treatment protocol guidelines, have been healthy, conditioned and fully vaccinated.

Because the McChesney reference includes no scientifically valid experimental procedures for assessing anti-viral or anti-bacterial effects of leflunomide, it cannot properly be held to teach the use of leflunomide products for inhibiting viral replication.

Likewise, the ordinarily skilled worker would find no credible basis for holding the Coghlan reference to teach the use of isoxazole compounds structurally related to leflunomide to inhibit viral replication. First and foremost, Coghlan addresses the synthesis of compounds "having immunomodulatory activity" (page 1, lines 6-7). Reference to disease states assertedly treatable with such immunomodulatory agents (page 3, line 1 to page 4, line 30) involves a shopping list of virtually every conceivable illness having a direct or indirect immunological component, and concludes with reference to a few viral diseases. Not one single scientific publication is cited for a showing of efficacy of leflunomide or structurally related isoxazoles in any such disease states. The sole assay for biological activity (Example 295) is a mixed lympocyte reaction test, having no connection whatever to assessment of anti-viral activity.

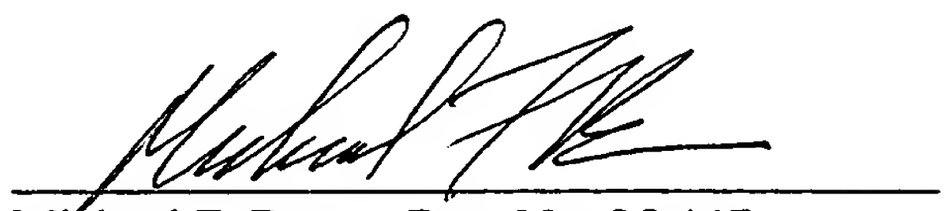
Clearly then, the McChesney and Coghlan references, alone or in combination, provide the skilled worker with no hint whatever that leflunomide products had been found to be effective in inhibiting viral replication or should be studied for such effect with any reasonable expectation of success.

IV. CONCLUSION

The foregoing is believed to establish that claims 16-25 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By 

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